

Remarks

Rejection Under 35 U.S.C. § 112 ¶ 1

Claims 1, 6, 86, and 87 are rejected under 35 U.S.C. § 112 ¶ 1 as lacking written description for the full scope of the recited polypeptides. To advance prosecution, independent claim 1 is amended to recite that the first and second polypeptides consist essentially of the recited components. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 1, 6, 86, and 87 are rejected under 35 U.S.C. § 112 ¶ 2 because the terms “first” and “second” polypeptide allegedly are indefinite. Applicants respectfully traverse the rejection.

Independent claim 1 is directed to a phage particle displaying on its surface a dimeric T-cell receptor (dTCR). The dTCR comprises two polypeptides. For convenience, the two polypeptides are referred to in claim 1 as “a first polypeptide” and “a second polypeptide.” There is nothing confusing about this terminology which, as evidenced by the sampling of claims below, is often used in claims directed to dimeric proteins:

- claim 12 of U.S. Patent 5,652,337 (“An isolated dimeric protein comprising a first polypeptide . . . , and a second polypeptide”);
- claim 4 of U.S. Patent 5,849,877 (“A dimeric polypeptide that binds to a human tumor cell displaying a multiple-drug resistance, said dimeric polypeptide comprising: a) a first polypeptide domain . . . ; and b) a second polypeptide domain”);
- claim 1 of U.S. Patent 6,663,870 (“A method for promoting proliferation of cells comprising culturing the cells in an effective amount of a dimeric protein comprising a first polypeptide chain disulfide bonded to a second polypeptide chain”);

- claim 18 of U.S. Patent 7,267,972 (“A process for making a polypeptide comprising . . . (a) preparation of an expression vector comprising . . . a recombinant nucleic acid encoding a dimeric protein having glycerol dehydratase activity comprising a first polypeptide . . . and a second polypeptide . . .”);
- claim 1 of U.S. Patent 7,381,794 (“A dimeric protein consisting of a first polypeptide fusion disulfide bonded to a second polypeptide fusion . . .”); and
- claim 1 of U.S. Patent 7,491,384 (“A method for promoting growth of bone, ligament, or cartilage in a mammal comprising administering to said mammal a composition comprising: a pharmacologically effective amount of a dimeric protein comprising a first polypeptide chain disulfide bonded to a second polypeptide chain . . .”).

Claims 1, 6, 86, and 87 as written are definite. Please withdraw the rejection.

Rejections Under 35 U.S.C. § 103(a) Over Weidanz I or Weidanz II

The Final Office Action rejects claims 1, 6, 86, and 87 under 35 U.S.C. § 103(a) as obvious over Weidanz I (*J. Immunol. Methods* 221, 59-76, 1998) or Weidanz II (WO 99/18129) in view of Reiter (*Immunity* 2, 281-87, 1995). Applicants respectfully traverse the rejections.

The U.S. Patent and Trademark Office bears the initial burden of establishing a prima facie case of obviousness based on the results of the factual inquiries under *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). M.P.E.P., 8th ed., § 2142. It remains black letter law that obviousness requires at least a suggestion of all of the features in a claim. See *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). Moreover, as the Supreme Court recently stated, “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 418, 127 S. Ct. 1727, 1741 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

As an initial matter, to advance prosecution claim 1 is amended to delete the single chain embodiment.¹ The present claims are now directed to a phage particle which displays on its surface a dimeric TCR (dTCR).

Phage display of dimeric proteins requires that one of the protein chains be expressed fixed to the coat protein of the phage particle, and the other expressed as a free protein. The free protein must then associate with the phage-fixed protein in a properly folded functional manner. It was known in the art that the alpha and beta chains of heterodimeric TCRs have a very low pairing efficiency. For years, this poor interchain binding affinity hampered attempts to produce soluble heterodimeric TCRs. If one expresses the chains separately (as one must) and attempts to refold the chains to produce the TCR, the heterodimer simply falls apart. In contrast, the two chains of an antibody have a very high pairing efficiency. There is no difficulty in refolding two antibody chains to form a soluble antibody, the resultant refolded heterodimer is extremely stable.

The phenomenon of poor pairing efficiency of TCR chains was widely recognized. For example, see Chang *et al.*, *Proc. Natl. Acad. Sci. USA* 91, 11408-22, 1994 (“Chang”) and Pecorari *et al.*, *J. Mol. Biol.* 285, 1831-43, 1999 (“Pecorari”), both provided with the accompanying IDS:

- Chang, Abstract: “Generation of soluble T-cell receptor (TCR) molecules by a variety of genetic engineering methods has been hampered by inefficient pairing

¹ Because this amendment deletes the single chain embodiment from the present claims, it is not necessary to discuss phage display of single chain proteins. However, even with this embodiment proper folding of the protein is still required for functionality on the phage particle. Expression of a single chain TCR still requires the V α and V β domains to fold correctly, and as is made clear by the quotations from Chang and Pecorari, discussed below, the binding interaction between those domains is extremely weak, especially in the absence of the two constant domains. Hence, achieving phage display of a properly folded single chain TCR was neither trivial nor obvious.

of α and β subunits in the absence of their respective transmembrane regions and associated CD3 components.”

- Chang, page 11408, col. 1, 9 lines from bottom: “Prokaryotic expression has yielded substantial quantities of TCR protein, which, unfortunately, comprise a very low fraction of native or correctly folded material.”
- Chang, page 11408, col. 2, line 2: “A maior problem with each of these strategies is the inefficient pairing between α and β subunits.”
- Chang, page 11410, col. 2, paragraph commencing at line 3: Just before the sequence it is said “the majority of α and β proteins are present as monomers . . . and thus do not associate with each other.”
- Pecorari, page 1832, col. 1, bottom of page: “However, attempts to refold TCRs in vitro or to express them functionally, whatever their sequences or formats, encountered great difficulties in many laboratories.”
- Pecorari, page 1832, col. 2, under “General Considerations”: “Preliminary experiments with refolding a series of TCR constructs of different T-cell clones . . . have led us to the conclusion that no published method or format of the recombinant TCR . . . appeared to be of general utility. Great differences between the aggregation tendencies of different TCRs became apparent.”
- Pecorari, page 1836, col. 2, line 21 from bottom: “Considering the large interaction surface between $V\alpha$ and $V\beta$ and $C\alpha$ and $C\beta$, this dissociation constant is quite high, especially when compared with the corresponding K_D observed for heavy and light chains in Fab fragments”
- Pecorari, page 1836, col. 2, line 8 from bottom: “this weak affinity between the α and β chains may be related to the more polar constant domain interface in the TCRs compared with the more hydrophobic one in antibodies.”
- Pecorari, page 1837, col. 1, last paragraph: “Since the interaction energy between the whole α -chain and the whole β -chain is already so weak”

Given the known poor association affinities between the α and β chains of a TCR (evidenced by the Chang and Pecorari quotations above), it is not surprising that phage display of

a dimeric TCR had not been demonstrated prior to the present invention. Again, we stress that similar difficulties do not exist with antibodies. Phage display of dimeric Fab fragments is routine because of the high binding energy between the two chains.

The dTCR recited in claim 1 comprises two polypeptides. One polypeptide consists essentially of a TCR α chain variable domain sequence fused to the N terminus of a TCR α chain constant domain extracellular sequence. The other polypeptide consists essentially of a TCR β chain variable domain sequence fused to the N terminus of a TCR β chain constant domain extracellular sequence. The constant domains are linked by an interchain disulfide bond. In the present invention, the provision of cysteines in the constant domain which form the interchain bond is the novel feature which enables successful pairing of the two chains. Without that feature, the poor interchain binding affinity causes any association which might form between the phage linked and free chains to be temporary and reversible. The interchain bond also facilitates proper functional folding of the phage displayed dimer, by holding the two chains in close proximity during the folding process. The recited interchain bond is neither taught nor suggested by either of the Weidanz references, either alone or in combination with Reiter.

The disclosures of the Weidanz I and Weidanz II were discussed in Applicants' previous response. On page 6 ¶ 2 of the Office Action, the Examiner asserts that Weidanz I discloses phage displayed dimeric TCRs. That is not correct. The Office Action specifically points to the following portions of Weidanz I:

Abstract: The Abstract mentions only single chain TCR phage display.

Page 60, col. 1: Page 60, col. 1 does not disclose phage display of dimeric TCRs. In fact, the paragraph at the bottom of page 60, col. 1 states:

In contrast to the success of phage-display systems for Abs (ie antibodies) display of alpha/beta TCR molecules on the surface of phage has not been successfully achieved. ... The lack of success is the result of technical problems associated with the expression of soluble TCR in E. coli

Weidanz I therefore confirms what has been said above in the discussion of Chang and Percorari.

page 60, col. 2: The mention of DO11.10 as a heterodimeric TCR is simply a reference to the parental TCR which Weidanz is going to reform as a single chain TCR for phage display. The authors obviously did not even contemplate the phage display of the parental heterodimer, because they, like the rest of the art, believed that the weak interchain binding energy of TCRs would prevent proper display.

page 73, col. 1: Again, in this portion of Weidanz I there is no mention of dimeric TCR phage display. This column discusses the possible factors influencing the proper folding of the three domain single chain TCR. Nothing here assists in solving the problem of proper functional display of a heterodimeric TCR.

As discussed in Applicants' previous response, Weidanz I is concerned exclusively with phage display of single chain TCRs. On page 9 of the Office Action the examiner asserts that it would be within the ordinary skill in the art to fuse "said heterodimeric TCR" to a phage because this has been done for single chain TCRs. First, the discussion above explains why that is not the case. Second, a statement that modifications of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (B.P.A.I 1993). Thus, "there must be some articulated reasoning with some rational underpinning to support the

legal conclusion of obviousness.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Here, the Office Action provides no reason why the skilled artisan would modify the single chain constructs of Weidanz I to arrive at Applicants’ claimed subject matter. Rather, the Office Action merely asserts that the application of ordinary skill is enough to render claims 1, 6, 86, and 87 obvious. This conclusory statement is not the articulated reasoning required under *KSR Int’l*.

Applicants also discussed the other primary reference, Weidanz II, in the previous response. Weidanz II does not add anything to the disclosures of Weidanz I. The secondary reference, Reiter, is discussed in the present specification in the paragraph at page 5, lines 11-21:

Reiter *et al*, Immunity, 1995, 2:281-287, details the construction of a soluble molecule comprising disulphide-stabilised TCR α and β variable domains, one of which is linked to a truncated form of *Pseudomonas* exotoxin (PE38). One of the stated reasons for producing this molecule was to overcome the inherent instability of single-chain TCRs. The position of the novel disulphide bond in the TCR variable domains was identified via homology with the variable domains of antibodies, into which these have previously been introduced (for example see Brinkmann, *et al.* (1993), Proc. Natl. Acad. Sci. USA 90: 7538-7542, and Reiter, *et al.* (1994) Biochemistry 33: 5451-5459). However, as there is no such homology between antibody and TCR constant domains, such a technique could not be employed to identify appropriate sites for new inter-chain disulphide bonds between TCR constant domains.

Reiter does not relate to phage display. It is entirely unknown whether the Reiter construct would refold functionally in the expression bacterium if one of the variable domains were expressed fixed to the phage coat protein, and the other variable domain were expressed free. The present invention requires both constant domains to be present, and positions an interchain bond between cysteines in the constant domain. By locating the interchain bond well away from

the variable domains, the present invention enables the TCR to refold with the variable domain in a completely natural functional configuration. Even if the Reiter construct were to assemble if expressed in a phage display system, the bond would be between residues in the variable domains and inevitably would induce a less than natural refold.

The prior art – including the cited Weidanz and Reiter references – is silent on how to ensure successful expression of phage particles displaying functionally folded heterodimeric TCRs. The references relied on by the examiner do not contain the slightest hint that the provision of an interchain disulfide bond between constant regions would enable what had not been previously available, namely successful phage display of dimeric TCRs.

Please withdraw the rejection.

Rejection of Claims 1, 6, 86, and 87 Under 35 U.S.C. § 103(a) Over Boulter

The Final Office Action rejects claims 1, 6, 86, and 87 under 35 U.S.C. § 103(a) as obvious over Boulter (Protein Eng.) in view of Schumacher (EP 1 118 661). Applicants respectfully traverse the rejection because Boulter is not prior art to the present application.

Boulter was published in September 2003. The present application claims priority to five GB applications and one US provisional application, each of which was filed before September 2003. Certified copies of the foreign priority applications are in the Image File Wrapper for the present application. The subject matter of claims 1, 6, 86, and 87 is supported fully in at least GB0316356.5, which was filed July 11, 2003. Display of dimeric TCRs on phage particles is disclosed throughout GB0316356.5, for example at page 12, line 15 to page 15, line 7; at page 29, lines 1-14; and in Example 4. Dimeric TCRs with the features recited in claim 1 are disclosed, e.g., at page 16, lines 1-14; at page 19, line 29, to page 20, line 7. Use of native

interchain disulfide bonds (encompassed within claims 1 and 6) and non-native interchain disulfide bonds (encompassed within claims 1 and 6 and explicitly recited in claims 86 and 87) are disclosed at page 19, line 29, to page 20, line 7. Linkage by a peptide bond of the C terminus of one member of the cTCR to a surface exposed residue of a phage particle (recited in claim 6) is disclosed at page 14, lines 21-25.

Because Boulter is not prior art to the present application, it cannot serve as a reference under 35 U.S.C. § 103(a). Please withdraw the rejection.

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